Risk-Based Recommendations for Mammographic Screening for Women in Their Forties

By M. Gail and B. Rimer

Purpose: **To develop risk-based recommendations for mammographic screening for women in their 40s that take into account the woman's age, race, and specific risk factors.**

Methods: **We assumed that regular mammographic screening is justified for a 50-year-old woman, even one with no risk factors, and that a younger woman with an expected 1-year breast cancer incidence rate as great or greater than that of a 50-year-old woman with no risk factors would benefit sufficiently to justify regular screening. Recommendations under this criterion were based on age- and race-specific breast cancer incidence rates from the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) Program; assessments of risk factors from the Breast Cancer Detection and Demonstration Project (BCDDP); and reports in the literature.**

Results: **Two methods, the exact-age procedure (EAP) and the grouped-age procedure (GAP), were developed. The less precise GAP only requires following a flow diagram. The proportion of white women recommended for screening by the EAP ranges from 10% for 40-year-old women to 95% for 49-year-old women, and the corresponding percentages for black women are 16% and 95%. The assumptions that underlie the guidelines are discussed critically.**

Conclusion: **For women or physicians who prefer an individualized approach in deciding whether to initiate regular mammographic screening in the age range of 40 to 49 years, the present report offers recommendations based on individualized risk-factor data and clearly stated assumptions that have an empiric basis. These recommendations can be used to facilitate the counseling process.**

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ALTHOUGH IT IS WIDELY ACCEPTED that women 50 years of age and older should have regular mammographic examinations to screen for breast cancer, opinion has been divided on whether women in their 40s should be screened regularly.[1,2] The American Cancer Society (ACS)[3] and the National Cancer Institute (NCI)[4] recently endorsed universal screening for women in their 40s, whereas members of a Consensus Development Panel on mammography sponsored by the National Institutes of Health in January 1997 concluded that, although there was some survival benefit, "the available data did not warrant a single recommendation for all women in their forties."[5] They recommended that women should make their own decisions, in consultation with health professionals. The US Preventive Services Task Force has not recommended routine mammograms for average-risk women in their 40s,[6] although many other organizations have endorsed such screening.

At the 1997 National Institutes of Health Consensus Development Conference on Breast Cancer Screening for Women Ages 40 to 49, Hendrick et al[7] showed an 18% reduction in breast cancer mortality rates based on a meta-analysis of the randomized trials of mammography, with a 95% confidence interval (CI) of 3% to 29%. Berry[8] combined data from seven randomized controlled studies of women in their 40s and calculated that the reduction in mortality rate for screened women was 17% (95% CI, 3% to 29%), based on the Mantel-Haenszel method of combining data under the assumption of homogeneity of screening effects over studies. Berry[8] noted that if it is assumed that the true benefit of screening may vary across study sites, there is greater uncertainty in the estimated CI, which may even include the possibility of no benefit. The ACS cited a mortality reduction of 18% (95% CI, 5% to 29%) in its report on Workshop Guidelines for Breast Cancer detection.[3] Although opponents of a general recommendation for screening of women in their 40s usually agree that there is some reduction in mortality rates, they conclude that the size of the benefit does not warrant a recommendation for universal screening.

What causes many observers to hesitate to recommend universal screening of women in their 40s is the relatively low chance of developing breast cancer in that age group and the high proportion of false-positive mammographic results,

From the National Cancer Institute, Division of Cancer Epidemiology and Genetics; and the Division of Cancer Control and Population Sciences, Rockville, MD.

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Address reprint requests to M. Gail, MD, PhD, National Cancer Institute, 6130 Executive Blvd, EPN/431, Rockville, MD 20892; Email gailm@epndce.nci.nih.gov.

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with attendant adverse effects of follow-up diagnostic procedures and anxiety among screened women.[9,10] Perhaps one third of women in a screening program for 10 years will require follow-up procedures, such as physical examinations, repeated mammograms, ultrasound examinations, or biopsies to rule out cancer.[11] Moreover, perhaps one quarter of the malignant histologies detected will be ductal carcinoma in situ (DCIS).[12,13] Although some question whether DCIS requires early intervention for adequate control, it is usually treated.[14]

There is increasing emphasis on the need for counseling to assist women to make informed health decisions. An informed decision regarding mammography would require that the woman understand the evidence about the efficacy of screening to reduce mortality from breast cancer, her own individualized risk for developing breast cancer over defined age intervals, and the limitations, inconveniences, and risks of screening, which include the need to evaluate abnormal results. Such a discussion would be complicated by scientific uncertainty about the efficacy of mammography for women in their 40s, by the virtual absence of data on efficacy from controlled randomized trials for women with particular combinations of risk factors (it is unlikely such data will ever be available), and by uncertainty in the ability to project individualized risks for breast cancer. Moreover, even if there was precise agreement on the risks and benefits of mammography for women aged in their 40s, women who consider the use of mammography might differ in the relative values or utilities that they place on the various adverse effects, such as the inconvenience and anxiety associated with mammography and attendant follow-up procedures and the expected survival benefit. For some women, the psychologic stresses or inconvenience might outweigh the expected survival benefit, whereas other women with the same risk factors and age might be willing to accept both screening and potential follow-up procedures to obtain a slight expected survival advantage. Health professionals who advise women about screening also place various values on the adverse effects and benefits of screening. Harris and Leininger[9] advised that these considerations be used in counseling women about mammography. In principle, the ideal screening recommendation would be one that reflected each woman's individual risks, perceptions of the efficacy of mammography, values, and preferences.

The difficulties of arriving at an informed individualized decision should not be underestimated. Many women would not have access to the expert guidance needed to assess individual risk factors, convey information on efficacy, and elicit values and preferences, and many women and their health care providers would not have the quantitative skills to accurately interpret data on risk and efficacy and on their uncertainty. A variety of assumptions about the risks and benefits of screening for women with specific risk factors would be required, and these would not always be explicit. These difficulties and accumulating evidence of modest benefit for women aged in their 40s may explain the recommendation for universal screening for women in their 40s by the ACS, the NCI, and other organizations.

The purpose of the present report is to offer risk-based recommendations for mammographic screening for women in their 40s. These recommendations take individualized risk factors into account and can be used as a point of departure for a more thorough, individualized discussion of a woman's particular risks and preferences. Our screening recommendations follow from assumptions that we will define and attempt to justify.

To develop mammography recommendations, we identified women with individual risk factors and an estimated risk for cancer incidence high enough to warrant screening in their 40s. Women at higher risk for cancer incidence are expected to have a higher absolute survival benefit and a higher prevalence of detectable disease, which will increase the positive predictive value of mammography. Both these factors would improve the benefit–adverse effect ratio of screening.[10]

We used as our benchmark a 50-year-old woman without risk factors. We assumed that all women 50 years of age or older should be screened, even the benchmark 50-year-old women with no risk factors. This assumption is consistent with the recommendations of all medical organizations that have made recommendations on mammographic screening. Therefore, we propose the following criterion: any woman in her 40s should be screened if she has the same or higher risk, judged by the risk factors discussed in Methods, as a 50-year-old woman with no risk factors. Separate calculations are required for black and white women because of differences in breast cancer incidence rates among women younger than 50 years of age.

Some may object to the use of a 50-year-old woman without risk factors as the benchmark on the grounds that evidence for screening efficacy for those aged 50 years or older was obtained by the study of populations of women with various risk-factor profiles and ages. If a higher benchmark were chosen, such as a 55-year-old women at average risk, fewer women in their 40s would be recommended for screening. In our view, however, an unacceptable consequence of the use of such a higher benchmark would be that these same procedures would lead to a recommendation not to screen many women in their 50s.

Thus, logical consistency with the accepted standard to screen all women in their 50s leads us to use the 50-year-old woman without any risk factors as our benchmark.

We present the assumptions and methods to make individualized recommendations for screening in the next section, illustrate these methods, give data on the proportion of the population recommended for screening under these guidelines in Results, and then discuss the assumptions and reasonableness of the approach and ways this information can be used to counsel patients. In particular, assumption 2 entails an assessment of the risks and benefits of screening women in their 40s and is considered at length in Discussion and Appendix.

METHODS

The screening recommendations are based on the following assumptions: (1) A 50-year-old woman without any risk factors should be screened with mammography, (2) a woman in her 40s whose risk factors give her a projected 1-year risk at least as great as that of a 50-year-old woman with no risk factors will benefit sufficiently to justify mammographic screening, (3) attributable risk for risk factors used in the model by Gail et al[15] remains constant between the ages of 40 and 50 years, and (4) relative risks estimated for white women also apply to black women, and, in particular, the relative risk model derived by Gail et al[15] from white women in the Breast Cancer Detection and Demonstration Project (BCDDP) also applies to black women. (This assumption is needed only for the relative-risk model. Age-specific rates are estimated separately for white and black women.)

As elaborated in the next section, it follows from these assumptions that a woman will be recommended for screening if her favorable relative risk (FRR) from being younger than 50 years of age is less than her adverse relative risk (ARR) from having specific risk factors.

Exact-Age Procedure

We first compute an FRR based on the age of the subject. The FRR is the ratio of the age-specific breast cancer incidence rate for a 50-year-old woman divided by the corresponding age-specific rate for a woman of the same age as the subject (Table 1). Note that the FRRs are usually larger for white than for black women because age-specific incidence rates increase faster in young black women than in young white women. Age-specific breast cancer rates for all malignancies, which includes DCIS, are based on data from 1988 through 1992 in the Surveillance, Epidemiology, and End-Results (SEER) program of the NCI. Before computing FRRs, these year-specific rates were smoothed by fitting a cubic spline[16] with knots at 25, 45, 55, and 75 years and with discontinuous second derivatives at 45 and 55 years. The smoothed rates fit the original data well but show smaller year-to-year variability (data not shown).

Table 1. FRRs From Younger Age Compared With Age 50 Years

Age, Years	White	Black
40	2.46	1.97
41	2.15	1.75
42	1.89	1.58
43	1.67	1.44
44	1.49	1.32
45	1.32	1.23
46	1.20	1.16
47	1.11	1.10
48	1.06	1.06
49	1.02	1.03
50	1.00	1.00

Table 2. Strong Risk Factors, Any of Which Justifies Regular Screening

1. Previous breast cancer in woman[24]
2. Woman has a disease-causing mutation in a breast cancer susceptibility gene, such as BRCA1 or BRCA2[25,26]
3. Mother, sister, or daughter with breast cancer history[15]
4. Atypical hyperplasia found on any previous breast biopsy[15]
5. At least 75% dense tissue on mammogram at age 45-49 years*[27,28]
6. Two or more breast biopsies, even if results are benign[15]

*Refers to the ratio of the area of dense tissue to the total area of breast tissue seen on the mammogram. Further comments that justify the age restriction are in the Discussion section.

Some women (Table 2) have ARRs that are believed to exceed every FRR in Table 1. Therefore, screening is recommended for women with any of the risk factors listed in Table 2. Citations in Table 2 support these criteria.

For women who do not have any of the risk factors listed in Table 2, the ARR can be computed by multiplying three numbers that correspond to age at menarche, number of previous breast biopsies, and age at first live birth or nulliparity (Table 3). The ARR is the product of these three numbers, and if the ARR equals or exceeds the FRR in Table 1, the subject is recommended for screening. The factors listed in Table 3 are from the study by Gail et al[15] of risk factors in the BCDDP.

Grouped-Age Procedure

An alternative simplified procedure that approximates the exact-age procedure (EAP) is to group women into age groups of 40 to 44 years and 45 to 49 years and to apply the decision-flow diagrams in Figs 1-3. We call this the grouped-age procedure (GAP) because it does not account for the age of the subject as precisely as the EAP. Decision-flow diagrams for GAP were constructed by calculating an FRR for each age group as the ratio of the smoothed age-specific incidence rate for age 50 years divided by the average of the five smoothed age-specific incidence rates for ages 40 to 44 and 45 to 49 years. Then, all risk-factor

Table 3. Factors to Calculate ARR for Women With None of the Conditions in Table 2

	Factor
Age at menarche, years	
≥ 14	1.000
12-13	1.099
< 12	1.207
No. of previous breast biopsies	
0	1.000
1	1.698
Age at first live birth, years	
< 20	1.000
20-24	1.244
25-29 or nulliparous	1.548
≥ 30	1.927

NOTE. Data from reference 15.

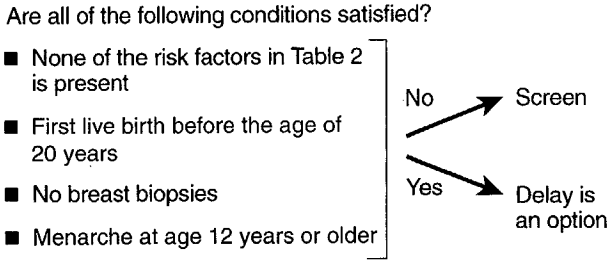

Fig 1. Flow chart for black or white women aged 45 to 49 years.

combinations were identified that had ARRs less than the grouped FRRs, and the decision-flow diagrams were constructed to identify those combinations as ones for which delayed screening seemed to be a reasonable option.

RESULTS

We show these methods by considering a nulliparous 44-year-old woman who began menstruation at age 12 years, who has had no breast biopsies, and who has had none of the conditions listed in Table 2. From Table 3, we calculate her ARR as $1.099 \times 1.000 \times 1.548 = 1.701$. If she is white, her FRR is 1.49 (Table 1), and if she is black, her FRR is 1.32. In either case, FRR is less than ARR, and the woman is recommended for screening by EAP. The ratio ARR/FRR indicates how close the woman's risk is to that of the benchmark 50-year-old woman. In this example, this ratio is 1.14 for a white woman and 1.29 for a black woman.

Suppose we apply the GAP instead. If the woman is white, we refer to Fig 2 and are led to suggest delay as an option. This example shows that the GAP need not always agree with the preferable EAP, because the FRR for the GAP is based on an average FRR for the 5-year age group, rather than for an exact age. Under the EAP, white women with these risk factors could be offered the option of delay at ages 40, 41, and 42 years and would be recommended for screening at ages 43 and 44 years (Table 1). In contrast, if the woman were black, the GAP (Fig 3) leads to a recommendation to screen, as does the EAP. We prefer the EAP, but the

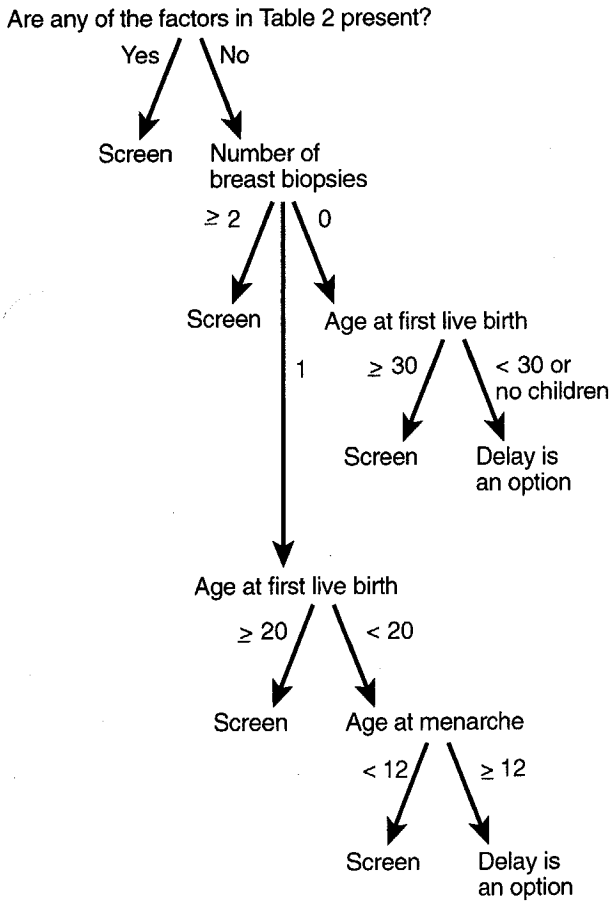

Fig 2. Flow chart for white women aged 40 to 44 years.

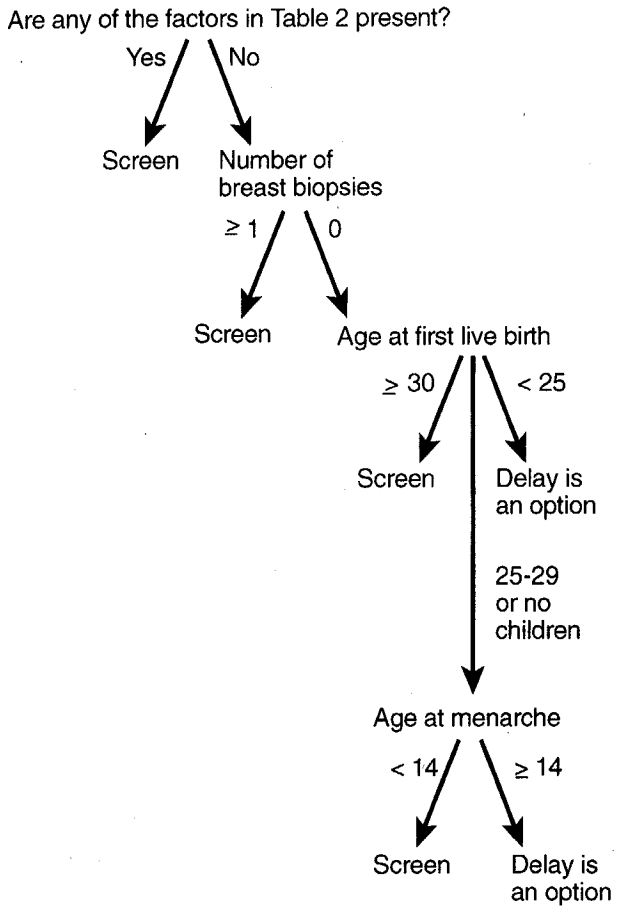

Fig 3. Flow chart for black women aged 40 to 44 years.

GAP will usually result in similar recommendations and may be easier to use.

Discrepancies between GAP and EAP are most likely to arise if the age of the woman is at the extreme ages of a group, namely 40, 44, 45, and 49 years. In particular, the GAP occasionally recommends screening for 40- or 45-year-old women for whom the EAP would recommend delay as an option, and the GAP occasionally recommends delay as an option for 44- and 49-year-old women for whom EAP would recommend screening. A detailed analysis of these discrepancies indicates that GAP agrees well with EAP, except at ages 43, 44, and 45 years. We recommend the EAP for women at these ages.

To estimate the proportion of women in the general population who would be recommended for screening by using these procedures, we analyzed data from the Cancer and Steroid Hormone Study (CASH).[17] The CASH study recruited patients with breast cancer and population-based controls from women aged 20 to 54 years. The joint distributions of the following risk factors were estimated separately from control women in the age ranges 40 to 44 years and 45 to 49 years: number of affected sisters or mother, age at menarche, number of previous biopsies, and age at first live birth or nulliparity. We grouped the data into 5-year age groups to obtain more stable estimates of the joint distributions of risk factors than would be possible if these distributions were estimated separately for each year of age. Assuming that factors 1, 2, and 5 in Table 2 were not present (factors 1 and 2 are rare, and factor 5 is usually not measured), we applied the GAP and EAP to these two distributions of risk factors to estimate the proportions of women who would be recommended for screening. For the EAP, the estimated proportions of white women recommended for screening ranged from 10% for 40-year-old women to 95% for 49-year-old women, and the corresponding range for black women was 16% to 95% (Table 4). More black women than white women are recommended for screening because the FRR is smaller for black than for white women younger than age 48 years (Table 1). The proportions recommended for screening under the GAP are 16% for white women aged 40 to 44 years, 84% for white women aged 45 to 49 years, 33% for black women aged 40 to 44 years, and 84% for black women aged 45 to 49 years (Table 4).

Table 4. Estimated Proportions Recommended for Screening for the EAP and GAP

Age, years	EAP, %		GAP, %	
	White	Black	White	Black
40	10	16	16	33
41	13	22	16	33
42	16	33	16	33
43	33	46	16	33
44	46	66	16	33
45	68	79	84	84
46	84	84	84	84
47	84	84	84	84
48	95	95	84	84
49	95	95	84	84

DISCUSSION

The ACS and the NCI now recommend regular mammograms for women in their 40s, although the recommended intervals differ (yearly for the ACS and every 1 or 2 years for the NCI).[3,4] Although policy recommendations must usually be made for large groups of people, such as women aged 40 to 49 years, it may be preferable to use individualized risk information to counsel women and make specific recommendations. Recently, the ACS modified its prostate cancer guidelines to reflect personal risk,[18] and both the ACS and the Agency for Health Care Policy and Research[19] included personal risk information in their colorectal cancer screening guidelines. Kerlikowske et al[10] mentioned the possibility of using individualized risk data to improve the positive predictive value of mammography for women aged in their 40s. Individualized risk information may also serve an important educational function for the large proportion of women who underestimate or overestimate their risk.[20,21] The present report follows trends toward informed, individualized decision making and provides an alternative to general screening guidelines by offering individualized recommendations that consider the woman's age, race, and adverse risk factors. To do this, we suggest two approaches: the EAP and the GAP. The EAP multiplies three numbers together to estimate the ARR and compares this product with the FRR from being younger than 50 years of age. The alternative GAP is less accurate than the EAP, especially at ages 43, 44, and 45 years, because the woman's precise age is not used, but the GAP can be implemented simply by referring to the decision diagrams in Figs 1-3.

One way to use such recommendations is as an invitation to discuss personal preferences and the risks and benefits of screening. For example, a woman at elevated risk who was not planning to have regular mammograms might reconsider the rationale for screening. This reconsideration might be prompted by her awareness that she was believed to be as good a candidate for screening as the benchmark 50-year-old woman without risk factors.

To provide guidance for Hispanic and Asian or Pacific Island women in the United States, we examined age-specific SEER incidence rates and computed FRR values, as

in Table 1. The FRR profile for Hispanic women resembles that for white women in Table 1, and the FRR profile for Asian and Pacific Island women resembles that for black women. The age-specific incidence rates themselves, however, are lower for Hispanic than white women and for Asian/Pacific Island than black women. If one is willing to assume that the relative risk features of the model by Gail et al[15] also apply to Hispanic and Asian/Pacific Island women and that 50-year-old Hispanic and Asian/Pacific Island women without risk factors should be screened, then the EAP and GAP procedures for white women can be used for Hispanic women, and the procedures for black women can be used for Asian/Pacific Island women. Recent immigrants from rural Asia are at much lower risk (see reference[22]) and warrant special consideration. Moreover, because the age-specific rate for a 50-year-old white woman, 291 per 10^5 person-years, is 69% greater than that for a Hispanic woman, 172, one may question the assumption that all 50-year-old Hispanic women should be screened. Likewise, the rate for a 50-year-old black woman, 244, is 23% higher than for an Asian or Pacific Island woman, 198.

In this report, we have proceeded on the assumption (assumption 1 in Methods) that the adverse effects and benefits justify screening for a benchmark 50-year-old woman without risk factors. This assumption is consistent with widely accepted screening guidelines from the ACS and the NCI, among other organizations. If, instead, we were to adopt as the benchmark an average 50-year-old woman, or an average 55-year-old woman, then the procedures we proposed would recommend that many women in their 50s not be screened. To avoid this inconsistency with currently accepted screening standards for women in their 50s, we adopted assumption 1. Ideally, there would be direct evidence from randomized studies of 50-year-old women without risk factors to show a favorable balance of beneficial and adverse effects for such a benchmark woman. Such data are not feasible to obtain, however, and the recommendations for such a woman will necessarily be based on previous studies of several populations of women older than 49 years of age.

At the request of a reviewer, we consider the use of a typical 50-year-old woman as the benchmark instead of a 50-year-old woman without any risk factors. Gail and Benichou[22] estimated the attributable risk in the CASH population as 0.398 for women younger than 50 years of age. Using this value as an estimate of the attributable risk from the risk factors in Tables 2 and 3 for the general population, we modify the FRRs in Table 1 for the new benchmark by multiplying each one by $1/(1 - 0.398) = 1.66$. Returning to the earlier example of a 44-year-old white woman with ARR = 1.701, we note that her FRR is now $1.49 \times 1.66 = 2.47$, and we would recommend delay as an option. Thus, using this new benchmark would cause fewer women to be recommended for screening. Note, however, that this benchmark would also cause us to recommend delay as an option to a 50-year-old white woman with an ARR less than 1.66, to a 55-year-old white woman with an ARR less than 1.51, and to a 60-year-old white woman with an ARR less than 1.25.

A second important assumption (assumption 2 in Methods) is that a younger woman whose risk factors imply an incidence rate as great or greater than that of a 50-year-old woman with no risk factors will also have a benefit to adverse-effect ratio sufficient to justify screening. We discuss this assumption in detail in the Appendix. The essential points regarding benefits are as follows. Current data suggest a mortality reduction from screening for women in their 40s of about 17% (95% CI, 3% to 29%) compared with 24% (95% CI, 12% to 31%) for women aged 50 to 74 years, which yields a benefit ratio of 17%/24% = 0.71. Assuming that the women younger than 50 years of age whom we recommended for screening have a breast cancer incidence rate at least equal to that of the benchmark 50-year-old woman without risk factors (this is the basis of our selection procedure), and assuming that the survival rates from the time of breast cancer incidence are no greater among the younger women, as available data suggest,[23] then the ratio of the reductions in absolute cancer mortality risks should also be at least 0.71. Thus, the benefit ratio (0.71), whereas somewhat more favorable to the benchmark woman than to younger women, does not weigh heavily against screening the younger women.

Regarding adverse effects, we adopt the point of view of women who consider screening. We make no attempt to evaluate costs in an economic model that compares a dollar spent on breast cancer screening with a dollar spent on prenatal care, for example. From the women's point of view, there are two principal adverse effects: the expense and inconvenience of routine screening and the anxiety, inconvenience, and costs associated with a mammographic result that requires further evaluation, which may include a biopsy. In the latter category, we count only adverse effects from false-positive mammographic results. We calculate (Appendix) that the ratio of adverse effects in women in their 40s recommended for screening to the benchmark 50-year-old woman is 1.01 for initial screens and 1.00 for subsequent screens.

Thus, a detailed analysis of benefits and adverse effects, although subject to uncertainty, suggests that the benefit–adverse effect ratio that compares young recommended

women to the benchmark 50-year-old women is at least 0.71/1.01 = 0.70. This figure is close enough to unity to warrant screening the younger women, in our opinion.

The possibility exists that some women in the population are unusually sensitive to radiation and might be harmed by exposure from mammography. Such harmful effects, if they exist, are outweighed by the overall survival benefits conferred by screening. Therefore, we do not explicitly account for such hypothetical instances of harm from mammography, which instead figure implicitly in the calculation of net survival benefits. Nonetheless, in the very rare situation in which a woman is known to carry a radiation-sensitizing mutation, the physician and counselee should consider this risk in devising a management plan.

Assumption 3 states that the attributable risk for factors in the relative-risk model used by Gail et al[15] remains constant for women between the ages of 40 and 50 years. Gail et al[15] showed that there was practically no difference in attributable risk for women younger than age 50 years and those 50 years and older in the BCDDP. The former had an attributable risk of 0.4771 and the latter 0.4736. Although the prevalence of biopsies and number of affected relatives may be smaller in younger women, the associated relative risks may be larger, which accounts for the nearly constant attributable risk. Constancy of attributable risk justifies the simple comparisons of ARR with FRR in the EAP and GAP methods.

Assumption 4 states that the relative-risk model derived from white women in the BCDDP[15] is also applicable to black women. Studies that involve large numbers of black women are needed to confirm this assumption. Only the relative-risk model used to calculate ARR is in question, however. The FRR calculations (Table 1) are race-specific.

Even accepting assumptions 1 through 4, one must consider the validity of the relative-risk models used to calculate ARR and of other risk factors in Table 2. Data that support items 1 and 2 in Table 2 are given in references 24 and 25, 26, respectively. Relative risks associated with items 3, 4, and 6 in Table 2 and all risk factors in Table 3 are based on data from the BCDDP.[15] When the BCDDP relative-risk model based on age at menarche, number of affected sisters or mother, age at first live birth, and number of previous breast biopsies was applied to independent data from the CASH study, similar relative-risk factors were obtained.[22] Because the CASH study was a population-based case-control study of women between the ages of 20 to 54 years from several regions of the United States, this confirmation of the relative-risk model increases our confidence in the methods used to calculate ARR (Tables 2 and 3). Item 5 is based on the publications of Byrne et al[27] and Boyd et al[28] that show relative risks for women with 75% or more dense breast images on the mammogram of 3.8 for women younger than age 50 years and 6.1 for women aged 40 to 49 years. Byrne et al[27] analyzed data from BCDDP, whereas Boyd et al[28] analyzed data from the Canadian National Breast Cancer Screening Study. Unpublished data from the BCDDP indicate that the relative risk is only about 1.5 for women aged 40 to 44 years and much larger for women aged 45 to 49 years (C. Byrne and R. Hoover, personal communication, May 1997), which is why we included mammographic density only for those aged 45 to 49 years in Table 2. Even for women aged 40 to 44 years, however, these associations are stronger than for some commonly used risk factors, such as age at menarche,[15] and mammographic density might contribute to models that contain other risk factors. Because such joint models are not yet available, however, mammographic density was not incorporated in Table 3.

It might be argued that the methods proposed in this report are passé after the recent recommendations of the ACS and NCI that all women aged in their 40s be screened.[3,4] A general recommendation for screening may be both necessary and appropriate for public health guidelines at the population level. However, individualized risk estimates are being used increasingly both for patient education and to guide clinical decision making,[18,19] ideally in a partnership between patients and clinicians.[9] Women who are reluctant to be screened may choose screening once they have been provided with information about their own risk. Other women who have high levels of anxiety about breast cancer risk may find personalized risk information reassuring[29] and may choose not to be screened. The risk-based screening recommendations included in this report can be used to promote further discussion of individual risks and preferences and to allow a woman in her 40s to compare her screening decision with that of a benchmark 50-year-old woman without risk factors.

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APPENDIX
Justification of Assumption 2

Assumption 2 (Methods) is that a woman younger than 50 years of age whose risk factors give her the same or greater risk of breast cancer incidence as a 50-year-old woman without risk factors will benefit sufficiently to justify mammographic screening. The benefit (B) to adverse-effect (AE) ratio (B/AE) hinges primarily on two issues: whether there is a substantial survival benefit for women recommended for screening in their 40s, and whether the rate of false-positive mammograms is tolerable in such women. On both these counts, there is reason to believe that the B/AE ratio is somewhat, although not markedly, less favorable in women recommended for screening in their 40s than for the benchmark 50-year-old woman without risk factors. For the following reasons, however, we believe that the ratio remains favorable enough to justify screening.

There is good reason to believe that screening women aged in their 40s confers a survival benefit. As previously mentioned, a meta-analysis of data from randomized controlled clinical trials for women in their 40s[7] indicates a mortality reduction of 17% (95% CI, 3% to 29%). A meta-analysis by Kerlikowske et al[30] that includes case-control data, as well as randomized clinical trial data for women aged 50 to 74 years, yielded an estimated mortality rate reduction of 26% (95% CI, 17% to 34%). We re-analyzed the data on the eight randomized clinical trials in Table 2 of Kerlikowske et al[30] for women aged 50 to 74 years. To perform this meta-analysis, we estimated the SEs of the log relative risk from log(ratio)/1.96, in which ratio is the upper confidence limit of the relative risk divided by the estimated relative risk in Table 2 of Kerlikowske et al.[30] We then performed a weighted least-square fixed-effects analysis on the log relative risk to obtain a summary estimate of the percent mortality rate reduction of 24% (95% CI, 12% to 31%). Thus, the estimated percentage reduction in mortality for women aged 50 to 74 is only slightly greater than that for women in their 40s, and there is considerable overlap in the CIs. A formal statistical test does not reject the null hypothesis that these two mortality reductions are equal (one degree of freedom $\chi^2 = 0.76$; $P = .38$). We conclude that the percentage of mortality reduction in women in their 40s is probably only a little smaller than that for older women, although the estimate is subject to considerable uncertainty.

Even if the percentage reduction in breast cancer mortality for women in their 40s were as great as that for a 50-year-old woman, the absolute reduction in mortality risk would be smaller for the younger woman because the cancer incidence rate is lower in younger women. However, women in their 40s who have an incidence rate at least as great as that of a 50-year-old woman without risk factors should, in the absence of screening, have an absolute mortality rate at least as great as that of the 50-year-old woman with no risk factors, because survival rates from cancer onset are, if anything, somewhat less favorable for younger women.[23] One concludes that screening the younger EAP-recommended women would attain at least $(0.17/0.24) \times 100 = 71\%$ of the reduction in absolute mortality risk as screening 50-year-old women without risk factors. Hence, whether one considers relative or absolute mortality reductions, one estimates a survival benefit ratio of at least $0.17/0.24 = 0.71$ that compares younger women recommended under EAP with a 50-year-old woman without risk factors.

Some have argued that the survival benefit derives not from screening women in their 40s but from subsequent screening as these cohorts age, because the survival benefit has been first shown only 8 to 10 years after screening begins.[2,5] Even if the benefits from initiating screening in women in their 40s are caused in part by other factors, such as later screening, one cannot dismiss the policy to initiate screening early as ineffectual.

To evaluate adverse effects from screening, we focus on false-positive screening results. The EAP and GAP seek to reduce the rate of false-positive results by recommending screening only to women in their 40s with elevated risks of breast cancer incidence. The false-positivity rate is 1 minus the positive predictive value,

$$PPV = P(D)sens/\{P[D]sens + P[\bar{D}][1 - spec]\},$$

where P(D) is the prevalence of breast cancer, $P(\bar{D}) = 1 - P(D)$, and sens and spec are the sensitivity and specificity of mammography. To be precise, sensitivity is the proportion of women detected by mammography to have breast cancer among women with this disease, and specificity is the proportion of women deemed not to have breast cancer by mammographic examination among women without breast cancer. For diseases with low prevalence, the positive predictive value is approximately

$$PPV = \sim P(D)\{sens/[1 - spec]\}. \quad (1)$$

From equation (1), the PPV can be increased and the false positivity rate decreased by screening women with higher breast cancer prevalence. Women with higher breast cancer incidence rates also have higher prevalence rates. In the steady state, prevalence = (incidence) × (average duration in the preclinical state). If the average duration in the preclinical state were the same for younger women as for a 50-year-old woman, then the strategy of selecting only younger women with risk factors that imply the same incidence rate as the older woman without risk factors would raise the prevalence of disease in the younger women to that among 50-year-old women without risk factors. In fact, Kerlikowske et al[10] found that prevalences of cancer at initial screening were 0.003 and 0.006, respectively, for women who are 40 to 49 and 50 to 59. The prevalence ratio, compared with the 40 to 49 year age group, was 2.00. Using SEER data from 1988-1992 for all breast cancers, including DCIS, and all races combined, we estimated overall incidence rates per 10^5 person-years of 190.3 and 303.3, respectively, for age groups 40 to 49 and 50 to 59. The corresponding incidence ratio, 1.59, is 20.5% smaller than the prevalence ratio, 2.00, perhaps because the mean duration of preclinical disease is shorter among younger women than older women.[31] On the basis of this analysis of prevalence and incidence data, we would expect that younger women with the same incidence rate as a 50-year-old woman without risk factors would have a 20.5% lower prevalence rate on the initial screen but a comparable prevalence rate on subsequent screens, which essentially detect incident disease. Thus, assuming similar sensivity and specificity of mammograms for younger and older women, we would estimate from equation (1) that the PPV for a 50-year-old woman without risk factors on the initial screen is equal to the PPV of the 50-year-old woman on subsequent screens.

Data from Kerlikowske et al[10] can also be used to assess the age dependence of the sensitivity and specificity of mammography.[32] For the initial mammographic screen, Kerlikowske et al[10] found that the specificity was nearly constant at 93% for those aged 40 years to older than 70 years. The

following calculations are virtually unaffected, however, even if we assume higher specificities in older women. Kerlikowske et al[10,32] reported age-specific sensitivities (based on cancers diagnosed within 13 months) of 86.7% (95% CI, 72.5% to 94.5%) for women aged 40 to 49 and 93.6% (95% CI, 81.4% to 98.3%) for women aged 50 to 59 years. Thus, the factor sens/(1 – spec) in equation (1) is in the ratio 0.867/0.936 = 0.926 for women in their 40s compared with women in their 50s.

Combining the effects of reduced prevalence and reduced sensitivity for women in their 40s recommended for screening by the EAP, we would anticipate from equation (1) that the PPV for the initial screen for the younger women would be 0.795 × 0.926 = 0.74 times that of a 50-year-old women without risk factors. For subsequent screens, the PPV would be 0.926 times the PPV of the 50-year-old women.

If we only count the adverse effects of false-positive results, the adverse-effect ratio that compares EAP-recommended women in their 40s to a 50-year-old woman without risk factors would be (1 – 0.74PPV)/(1 – PPV) for the initial screen, where PPV is the positive predictive value for a 50-year-old woman without risk factors. For subsequent screens, 0.74 would be replaced by 0.926 in this expression. Kerlikowske et al[10] (see their Table 5) give a PPV of 0.05 for women on their initial screening and 0.06 on subsequent screens. Therefore, the false-positive adverse-effect ratios are 1.01 for initial screens and 1.00 for subsequent screens. If one adds to the adverse effects of false-positive results the adverse effects of routine screening, these ratios are even closer to unity. Note that these calculations are very little affected by considerations of age-specific sensitivity and specificity because PPV is small compared with unity. We conclude from these considerations that the adverse effects of screening EAP-recommended women are similar to those of screening a 50-year-old woman without risk factors.

Finally, even assuming an adverse-effect ratio of 1.01, the estimated ratio of the survival-benefit ratio to the adverse-effect ratio is 0.71/1.01 = 0.70. Thus, there is a somewhat greater B/AE ratio for the 50-year-old woman without risk factors than for EAP-recommended women in their 40s. This number seems close enough to unity, however, to justify assumption 2.

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